B5 Cont.

peptide and the ligated nucleotide sequence is [and] expressed in an expression system [as a fusion protein].

Remarks

Rejections under 35 U.S.C. §112

The specification was objected to and claims 1-3, 5, 7, 8, 14, 15, and 17-21 were rejected under 35 U.S.C. §112 as non-enabled for an antibody binding to two sites. Claims 1-3, 5, 7, 8, 14, 15, and 17-21 were rejected under §112 as indefinite. These rejections are respectfully traversed if applied to the amended claims.

Enablement

The Examiner's comments regarding enablement raise a concern that there is a very basic concept that has not been clearly communicated by the undersigned regarding the claimed antibodies, both the original antibody as well as the recombinant claimed herein. The original antibody referred to as "HPC4" isolated by the Esmons is highly unusual. The declarations filed in support of the patentability of this antibody demonstrate that it is unique in recognizing the **combination** of a specific peptide epitope and calcium; in the absence of either, the antibody does not bind. Therefore the binding of the antibody is for two epitopes. By providing HPC4 originally, the Esmons enabled an antibody have dual specificity. The Examiner is correct that it would require undue experimentation to provide another antibody having this dual specificity. Accordingly, since HPC4 is a murine antibody and it is desirable to have humanized antibody fragments for use in therapeutic applications, the

HPC4 antibody gene was cloned. There could have been no expectation that it was possible to clone the hypervariable region responsible for this unusual characteristic of the antibody nor that recombinant antibody or fragments thereof would share this unique specificity. However, the genes were cloned as recited at pages 9-14 and in the sequence listing and expressed as described at pages 11-12. Experiments were conducted which demonstrate that Fabs for HPC4 were made in *E. coli* and have activity. The Examiner's attention is drawn to page 12 of the application, where these studies wherein the fragments were expressed in the bacteria and demonstrated to bind are described in detail. Applicants do not claim the light chain or heavy chain alone, only the nucleotide sequences encoding these regions.

Accordingly, the claims are enabled by the application.

Indefiniteness

With regard to the issue of indefiniteness, the Examiner's comments regarding the term "HPC4" in claim 1 are not understood. The murine antibody, including the hybridoma, was deposited with the American Type Culture Collection, as described in the earlier issued patent to Esmon, et al., and as referenced in the application and claims as originally filed. Since terms are interpreted in view of the specification, one skilled in the art would have no trouble understanding the meaning of "HPC4" antibodies. The phrase "wherein the antibody is not the HPC-4 antibody . . . " has been deleted from claim 1 to facilitate prosecution. It is clear that HPC4 as deposited with the ATCC is a murine antibody; claim 1 defines the claimed antibody as recombinant. This was previously rejected as not excluding HPC4,

although it should have done so since HPC4 is not recombinant and differences in glycosylation and amino acid sequence can be readily determined between the recombinant antibodies and the murine HPC4 antibody deposited with the ATCC. Claim 1 has also been amended to recite that the antibody is expressed in bacteria or contains human amino acid sequence. Support for these amendments is found for example at page 5 last paragraph, page 7, pages 11-12, and pages 14-17. The claim has also been amended to delete the reference to the nucleotide sequences and degenerate sequences to remove the objection regarding the term "degenerate" (which typically means that the nucleotide sequence is different but encodes the same amino acid sequence).

In response to the questions regarding the variable and constant region, the claims have been amended to define the antibody as including the hypervariable region of the murine HPC4 antibody; as discussed at pages 14-17, it is not essential to have the constant or even portions of the variable region to make a functional recombinant antibody. Claim 3 has been amended to recite that the antibody contains human sequence in the constant domain or framework regions of the variable domain, as described at page 15, lines 28-33.

With regard to the meaning of fusion protein and "different protein" as referred to in claims 20 and 21, the examiner's attention is drawn to the discussion in the application at page 17 relating to expression of the recombinant protein including other peptides such as a linker which couples the heavy and light chains together. The claims have been amended to more clearly define the claimed subject matter. Applicants are of course willing to amend

the language as the Examiner feels appropriate to reflect that the claims are directed to the hypervariable region of the antibody, alone or as part of additional antibody sequence, coupled to "non-antibody" amino acid sequence.

Obviousness-type double patenting

Claims 1-5, 7 and 8 were rejected under the doctrine of obviousness type double patenting over claims 1-3 of U.S. Patent No. 5,202,253 to Esmon, et al. Claims 14-19 were rejected under the doctrine of obviousness-type double patenting over U.S. Patent No. 5,202,253 to Esmon, et al., in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). These rejections are respectfully traversed.

The Examiner's position is that the nucleotide sequence is obvious from the prior disclosure of the protein, i.e., the HPC-4 antibody. This is contrary to the law.
In the absence of the nucleotide sequence, one could not make the claimed antibody. It was established by the Court of Appeals in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995) that merely having the protein, or even some amino acid sequence (which is not described in the claims of the issued patent) would not be sufficient. The examiner has cited no art that discloses or makes obvious the amino acid sequence encoded by the recited nucleic acid. The art which has been cited by the Examiner discloses general methods to make chimeric antibodies. This would not provide one skilled in the art with the methodology and a reasonable expectation of success that one could clone the hypervariable region of the HPC4

antibody, insert the cloned genes into an expression vector, and express antibody or antibody fragments having the requisite binding affinity. The Examiner's attention is again drawn to in re Deul, which specifically rejects this argument, on the basis that a "plan" is not enough to make obvious a nucleotide sequence. Even though the claimed subject matter is an antibody, the antibody **cannot be made except by expression of the nucleotide sequence**; accordingly, the antibody cannot be obvious from the naturally occuring antibody.

Rejections under 35 U.S.C. §102(b)

Claims 1, 2, 4, 5, 7 and 8 were rejected under 35 U.S.C. §102(b) and (e) as disclosed by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638 to Esmon, et al. These rejections are respectfully traversed if applied to the amended claims. The claims have been amended in response to the rejections under §112, as discussed above.

Even prior to amendment, the claims specifically exclude HPC4 as deposited with the ATCC. This should have obviated this rejection. However, the claims have been amended to recite even more definitively that the claimed fragments are recombinant and either expressed in bacteria or including human amino acid sequence. Since HPC4 is a murine antibody expressed in a mammalian cell, these amendments clearly exclude the antibody described in the Esmon patents.

Rejections under 35 U.S.C. §103

Claims 1-3, 5, 7, 8, 14-15 and 17-21 were rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638 to Esmon, et al. in view of

Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). Claims 20 and 21 were also rejected under §103 as obvious over U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638 to Esmon, et al. in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen") and U.S. Patent No. 5,298,599 to Rezaie, et al. These rejections are respectfully traversed.

As discussed above, HPC-4 as it was deposited with the ATCC has been excluded from the claims. As evidenced by the testimony in the '253 case, numerous experts testified that even with undue experimentation they were unable to make by standard techniques monoclonal antibodies havin the unique specificity of HPC-4: binding with one part of the antibody a peptide epitope and binding with another part of the antibody calcium. Until one had actually cloned the nucleotide sequence encoding HPC-4 and expressed it, it was not possible to predict that the isolated nucleotide sequence encoded HPC-4, much less whether it would be expressed in functional form. Recombinant fragments have been expressed in bacteria and shown to have the requisite binding activity. Humanized antibodies having the same specificity have now been made using standard techniques, based on the disclosed nucleotide sequence, by Genentech. In the absence of the nucleotide sequence, one cannot modify and genetically engineer the antibody to include non-murine amino acid sequence.

There is no argument that the methods used by applicants were known. However, as the Court discussed in In re Deuel, merely having a plan is not enough. Applicants had attempted to make antibody fragments which had the requisite binding activity and found that

the cleavage reactions generated many products, with loss of most activity. The definition of the hypervariable region, which was determined by cloning, was critical to construction and expression of defined portions of HPC4 and to humanization of the antibody. One skilled in the art simply could not have any basis for determining whether or not an antibody with the unique specificity of the HPC4 antibody could be cloned and this specificity expressed in a recombinant molecule. The Examiner has cited no evidence that one skilled in the art had ever attempted to clone such an antibody, much less had any success. In summary, the art does not make obvious that the cloning and expression could be accomplished with a reasonable expectation of success. The comments on page 7 appear to support this argument.

U.S.S.N. 08/259,321
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AMENDMENT UNDER 37 C.F.R. §1.129a

Allowance of all claims 1, 3-5, 7, 8, 14, 15, and 17-2119 as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

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Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Transmittal Letter, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: January 30, 1997

Claims as pending upon entry of this amendment

1. (twice amended) A recombinant Ca^{2+} dependent monoclonal antibody or antibody fragment comprising the hypervariable region of the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 immunoreactive with a first epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) in combination with a second epitope consisting of calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin[, and wherein the antibody is encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID No. 9); CAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11); CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA

AGCTGGAAAT AAAACGG (nucleotides 67 to 387 of Sequence ID No. 11); and degenerate sequences thereof, and wherein the antibody is not the HPC-4 antibody deposited with the American Type Culture Collection as ATCC No. HB 9892], wherein the antibody is expressed in bacterial cells or contains human amino acid sequence.

2. (amended) The antibody of claim 1 comprising an amino acid sequence selected from the group consisting of:
MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

3. (twice amended) The antibody of claim 1 [containing] comprising human amino acid sequence [other than the sequence defining the epitope binding specificity] in the constant domain or framework regions of the variable domain.

5. (amended) A composition comprising the antibody of claim 1 in combination with a pharmaceutically acceptable carrier for administration to a patient.

7. The antibody of claim 1 having a detectable lable bound to the antibody.

8. (amended) The antibody of claim 1 immobilized to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

14. (twice amended) A method of making a recombinant Ca^{2+} dependent monoclonal antibody immunoreactive with a first epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) in combination with a second epitope consisting of calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin, by expressing nucleotide sequence encoding the [antibody, wherein the antibody is encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT

ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID No. 9); CAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (nucleotides 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11); CAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACTTACG TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACT CTTGATTTAT GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT AAAACGG (nucleotides 67 to 387 of Sequence ID No. 11); and degenerate sequences thereof, and is not HPC-4] hypervariable region of the monoclonal antibody expressed by the hybridoma [as] deposited with the American Type Culture Collection as ATCC No. HB 9892 in bacteria.

15. (amended) The method of claim 14 wherein the antibody comprises an amino acid sequence selected from the group consisting of:
MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT

FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

17. (twice amended) The method of claim 14 further comprising inserting human sequence into the antibody in [place of animal sequence other than the sequence defining the epitope binding specificity] the constant domain or framework regions of the variable domain.

18. The method of claim 14 further comprising binding detectable lable to the antibody.

19. (amended) The method of claim 14 further comprising immobilizing the antibody to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

20. (amended) [A] The recombinant [HPC-4] antibody [as deposited with the American Type Culture Collection as ATCC No. 9892 expressed as a fusion protein] of claim 1 having coupled thereto a peptide sequence.

21. (amended) [A] The method [for making a recombinant HPC-4 antibody wherein a nucleotide sequence encoding HPC-4 antibody as deposited with the American Type Culture Collection as ATCC No. 9892] of claim 14 wherein the nucleotide sequence encoding the recombinant antibody is ligated to a sequence encoding a [different protein] peptide and the ligated nucleotide sequence is [and] expressed in an expression system [as a fusion protein].